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Revising Sepsis Definitions to Better Target and Tailor Sepsis Care

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How we define sepsis has significant implications for clinical care, quality improvement, and regulatory policies. Current sepsis criteria identify heterogenous patients that vary widely in their clinical syndromes, triggering pathogens, and prognoses; one-third have viral or non-infectious processes and crude mortality rates vary 30-fold. Nonetheless, clinicians have been trained to treat all patients with possible sepsis immediately, aggressively, and uniformly with broad-spectrum antibiotics. Evidence continues to mount, however, that immediate antibiotics are only critical for patients with septic shock or multiorgan dysfunction while, patients with single organ dysfunction without shock can safely tolerate short delays until antibiotics. This allows time to clarify whether these patients are infected or not. We suggest modifying sepsis operational definitions to flag just those patients in whom short antibiotic delays are associated with increased mortality. This will help focus sepsis care where it is needed, aid antibiotic stewardship, and increase the validity of sepsis quality measures.

Keywords. sepsis; septic shock; sepsis definitions; time-to-antibiotics; quality improvement.

Sepsis is synonymous for most people with life-threatening infections that require immediate and aggressive treatment to preserve life. Clinicians, quality improvement leaders, and regulators have therefore launched wide-ranging initiatives to increase public and professional sepsis awareness, speed sepsis recognition, and standardize initial care to assure that all patients with possible sepsis receive a common and minimum set of interventions. The success and cohesiveness of these initiatives, however, depend upon how we define sepsis.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection" [1]. This definition makes good sense conceptually, but applying this definition at the bedside is challenging because clinicians have no way to measure the breadth and complexity of host responses, assess their regulation versus dysregulation, and determine whether dysregulation was triggered by infection or some other cause in anything approaching real-time at the bedside. The Sepsis-3 task force therefore proposed operational criteria for sepsis that clinicians can use as proxies for patients who may meet the conceptual definition of sepsis, namely, the combination of suspected infection plus organ dysfunction, quantified as an increase in Sequential Organ Failure Assessment (SOFA) score by ≥2 points. Many clinicians and researchers have adopted Sepsis-3 operational criteria for identifying sepsis. Others, including the US Centers for Medicare and Medicaid Services' SEP-1 measure, still use the Second International Consensus Definition (Sepsis-2), which defined severe sepsis as suspected infection, at least 2 systemic inflammatory response signs, and acute organ dysfunction, quantified using specific thresholds per organ [2].

In practice, however, both Sepsis-2 and Sepsis-3 operational definitions identify a very heterogenous set of patients that vary widely in their presenting syndromes, severities, prognoses, triggering pathogens, probability of true infection, and likelihood that organ dysfunction is due to infection versus some other cause [3–6]. Many do meet the sniff test for sepsis: they are critically ill with multiorgan dysfunction, have crude mortality rates over 20%, and would unquestionably succumb to their illnesses without immediate and aggressive care. A sizable fraction of patients flagged by current sepsis operational criteria, however, do not fit this pattern. One in 6 patients who meet Sepsis-3 operational criteria in the emergency department are well enough to be discharged home from the emergency department [7]. More than a third are hemodynamically stable and have only 1 organ dysfunction [6, 8]. Less than half require intensive care [8]. Less than 10% have drug-resistant pathogens that necessitate broad-spectrum antibiotics [9]. Crude mortality rates vary more than 30-fold across the syndromes identified

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by current operational sepsis criteria, from 1% for tickborne infections with thrombocytopenia to over 30% for cardiac infections with respiratory failure [6].

The very wide spectrum of illnesses captured by current sepsis operational criteria are problematic because clinicians and regulators have been taught to treat all sepsis patients in a common fashion with immediate broad-spectrum antibiotics, and for those with hypotension and/or elevated lactates, high volume intravenous fluids. Regulators and quality improvement advocates reinforce and accelerate this perception through public reporting and pay-for-performance metrics that penalize clinicians and hospitals for failing to administer these interventions within 3 hours of recognizing possible sepsis.

This would not be a concern if clinicians could quickly and accurately identify bacterial sepsis. In practice, however, differentiating bacterial sepsis from a host of mimicking syndromes can be very difficult, particularly in the heat of initial presentation. Approximately one third of patients treated with intravenous antibiotics for suspected bacterial sepsis turn out to have viral infections or non-infectious conditions (eg, acute heart failure, obstructive lung disease exacerbations, cancer, thromboembolic disease, drug reactions, drug withdrawal, toxidromes, etc.) [10–16]. These patients are exposed to the potential risks of antibacterials without their benefits.

What clinicians need in these circumstances is time to sort out infected from uninfected patients and bacterial from non-bacterial infections. To do so, however, we need give clinicians the time and space to work out these differences in the subset of patients in whom it is safe to do so. This in compels us to modify sepsis operational criteria to hone in on just the subset of patients that require immediate antibacterials and exclude the broader population in whom it is safe to take time to sort out infection from non-infection.

Fortunately, in the near decade since Sepsis-3 definitions were first released, multiple studies have helped elucidate how timing fits into antibiotic management for suspected sepsis. This has required recognizing and accommodating the many sources of bias that threaten the validity of observational studies of associations between time-to-antibiotics and mortality [17]. Many studies have reported that delayed administration of antibiotics is associated with higher mortality rates. But antibiotic timing for patients with possible sepsis is not random [18–20]. Patients with more obvious infectious presentations and more severe illnesses are treated with antibiotics sooner whereas those with more subtle, ambiguous, or complex presentations tend to get antibiotics later [21]. The latter group, however, tends to include more patients of advanced age, patients with multiple comorbidities, and more patients with cancer and other serious conditions that contribute to their higher mortality rates.

Studies that have carefully adjusted for these and other potential confounders suggest each hour is associated with increased risk of death in patients with septic shock and in patients with multiorgan failure but not in patients with less severe syndromes [18, 19]. Indeed, for some syndromes captured by current sepsis operational criteria, namely hemodynamically stable patients with a single organ dysfunction, intervals of 5 hours or more can safely be tolerated before mortality rates begin to rise [18–20]. In some patients with severe infections, mortality rates only begin to increase if antibiotic treatment is delayed >24 hours after infection recognition [22]. The safety of short antibiotic delays for patients with possible sepsis is further supported by two randomized trials that documented similar outcomes amongst patients treated immediately upon presentation versus patients treated a median of 73–96 minutes later [23, 24].

Indeed, from a pathophysiological point-of-view one would expect a dysregulated host response to infection to lead to multiple organ dysfunctions. The presence of just 1 organ dysfunction makes a systemic mechanism less likely. There are often multiple potential explanations for organ dysfunction in patients with possible sepsis in addition to the possibility of a dysregulated response to infection. Examples include dehydration or fluid loss leading to renal dysfunction or hypotension, adverse drug effects leading to hepatic, renal or hematologic dysfunction, hitherto unrecognized chronic organ dysfunction, exacerbations of known kidney, lung, or liver disease, and more. The probability that organ dysfunction is due to a non-infectious cause is likely greater among patients with just 1 organ dysfunction compared to those with refractory shock or multiple organ dysfunctions.

In light of these observations, professional societies have recommended modifying sepsis quality metrics and treatment recommendations to focus on just the subset of patients with shock [25, 26], but this approach is unlikely to be successful so long as sepsis operational definitions continue to apply the term “sepsis” to a broader set of patients. To do so would require clinicians to resist treating some patients with the label “sepsis” in the specific and aggressive manner we have been taught that we must treat all patients with sepsis.

We believe the solution is to modify sepsis operational definitions. Sepsis connotes for most people the necessity of immediate and aggressive action, and thus sepsis operational criteria should identify just those patients that require immediate and aggressive action. Patients with less severe syndromes in whom it is safe to take time to clarify the diagnosis should be excluded from sepsis operational criteria (or recategorized for prioritized but less rigid care). Modifying operational definitions for sepsis to just patients with suspected infection and shock or multiorgan dysfunction has the potential to improve outcomes by prioritizing immediate antibiotics for those who need them, prioritizing accurate diagnoses and non-sepsis care for patients without infection, and increasing the face validity and acceptability of sepsis quality improvement

initiatives and metrics by focusing them on the subset of patients who truly need immediate and aggressive care.

Note

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